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Implantable Devices for Chronic Access and Drug Delivery to the Central Nervous System

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ABSTRACT

This is a review of implantable devices for chronic access and drug delivery to the central nervous system (CNS) via the cerebrospinal fluid, extracellular fluid, and vascular pathways. The current applications of such devices in the management of mycotic meningitis, meningeal leukemia and carcinomatosis, solid malignant tumors of the CNS, intractable cancer-associated pain, unresectable cystic tumors and in cytologic, pharmacologic, and experimental studies on the cerebrospinal fluid (CSF) are assessed. Specific attention is paid to the applications of the most commonly used device, a subcutaneous reservoir and pump (SRP), including its major uses and complications. A new system for local chemotherapy of malignant gliomas, the tumor cyst device (TCD), is also described.

HISTORICAL INTRODUCTION

EARLY attempts to circumvent the blood-brain barrier by direct injection of drugs into the ventricular cerebrospinal fluid or brain tissue using spinal needles or temporary catheters were fraught with hazard if repeated procedures were required.[1] Our experience with such complications was obtained at the Radcliffe Infirmary, Oxford, in the course of treating cases of tuberculous meningitis. Patients were prepared for a series of intraventricular streptomycin injections at the request of Dr. Honor Smith using the following technique which was in common use at that time (1954–1960). Bilateral frontal burr-holes were made and after cauterization of the underlying dura and cortex, the scalp was closed, and repeated percutaneous punctures of the frontal horns of each lateral ventricle were carried out using a spinal tap needle. Although this technique was an improvement over open ventricular drainage with its attendant higher risk of infection, it suffered from the significant risk of intracerebral hemorrhages and porencephalic encephalomalacia along the cerebral puncture tracks. The concept of a *closed* system was, however, an attractive one and this idea bore fruit in 1962 at the Clinical Center of the National Institutes of Health, Bethesda, Maryland. We were faced with the problem of how to provide chronic intrathecal chemotherapy to a patient with cryptococcal meningitis whose spinal cerebrospinal fluid (CSF) pathways had become inaccessible due to archnoiditis following multiple spinal and cisternal taps. It was this experience that led directly to the development in 1963 of the first totally implantable and practical device for chronic drug access to the central nervous system (CNS) in humans.[2] In the first publication on this device, it was described as a subcutaneous reservoir and pump (SRP) (Fig. 1B and insert). The im-

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portance of the dual functions of *reservoir* and *pump* in this device must be emphasized because both aspects are not only required for proper usage but have also served as conceptual prototypes for recent advances in implantable systems for drug delivery.[3] Although the SRP device was introduced over 20 years ago for access to ventricular and spinal CSF primarily to give antifungal agents in the treatment of fungal meningitis, subsequent applications have been fairly wide, partic-

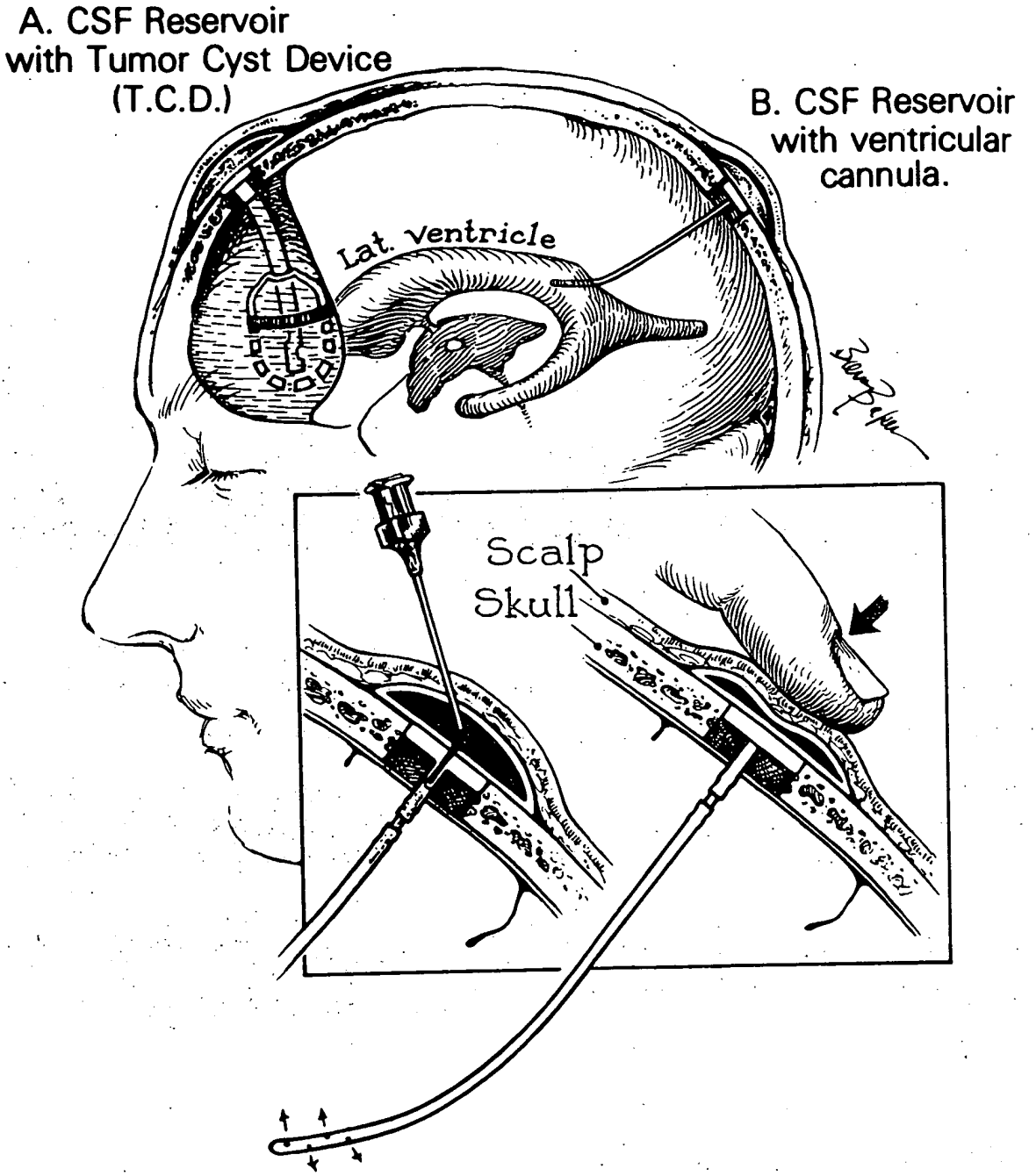

FIG. 1. Diagramatic view of subcutaneous resevoir and pump (SRP) device in place with an intraventricular catheter (B) and showing mode of injection with subsequent manual barbotage (*inset*). Also shown is the tumor cyst device (TCD) in place within a frontal tumor resection cavity connected to a SRP device (B). Note multiple performations in the TCD bulb, which maintains free fluid flow between the SRP and the extracellular environment of the tumor surfaces.

ularly in the treatment of a variety of CNS neoplasia both for prophylaxis and therapy.[4-9] There have been other attempts to develop similar access techniques; a recent example of such a prototypical idea (apparently unpublished until 1983 although used as early as 1952) is described by Heimbecker.[10] This device is very similar to the Rickham Reservoir, which has been available since 1964.[11] Both of these indwelling cannulae suffer from the disadvantage of not incorporating a pump component in their design, thus precluding non-invasive barbotage. We will discuss some of these applications and also some of the current modifications and extensions of the original SRP concept, particularly as they apply to the treatment of nervous system neoplasia.

TECHNIQUES OF RESERVOIR PLACEMENT AND USAGE[2,12,64]

The method described is the installation of the standard SRP device with a single exit on its flat-bottomed surface, the side-exit modification as well as the double-exit adaptation. After suitable preparation of the scalp (usually over the right frontal area), a semicircular incision is made with the curve of the small flap situated anteriorly behind the hair line. This incision effectively denervates the scalp area within the flap rendering subsequent punctures painless for a considerable time. After making a burr hole, the dura and subjacent cortex are carefully cauterized using bipolar coagulation, and the ventricular catheter is introduced. Some surgeons prefer to find the ventricle and guage the length of the ventricular catheter before placement of the device and catheter as one piece. Others use a stylet placed within the ventricular catheter to find and place the catheter in the frontal horn and then to connect the SRP device to the catheter. Whichever method is chosen it is important that only a short length of the catheter rests within the ventricle in order to avoid drift of the catheter tip into the third ventricle, unless that is deliberately planned for diagnostic or therapeutic purposes, e.g., as developed for contrast and radioisotope ventriculography by Hekster *et al.*[13] It is our practice to confirm proper positioning of the catheter tip by two X-ray films prior to closing the wound. This in important in preventing faulty intracerebral placement of the catheter. The device is ready to be used immediately and indeed we have routinely recommend early usage in all cases.

Transcutaneous puncture is done under strict aseptic conditions similar to a spinal tap. A short bevel needle (never larger than 23 guage and usually of the butterfly type) is introduced at an oblique angle to the dome surface. Aspiration must always precede introduction of any drug in order to obtain a pretreatment CSF sample as well as to prevent pushing in of a small skin plug and risk of CSF contamination. It is suggested that the aspiration specimen be removed and the syringe disconnected from the needle left *in situ* so that a fresh drug-containing syringe be connected for any further treatment. When reservoir punctures are repeated, it is our practice to select different sites for the sequential punctures following the numbers on a clock face beginning at 12 and proceeding in a clockwise manner. This method provides optimal efficiency in the self-sealing capacity of the silicon rubber dome of the reservoir. We have also shown that pumping the SRP device is an efficient means of ensuring that prior to drug introduction a representative sample of ventricular CSF is obtained; after drug injection, barbotage by reservoir pumping will cause maximum mixing of the drug with the remainder of the CSF after seven to eight pumps (Fig. 2).

CURRENT APPLICATIONS OF IMPLANTABLE DEVICES IN THE CNS

Mycotic meningitis

The first report on the clinical use of the SRP device was in 1964 when Witorsch *et al.* reported on their experience with the use of intraventricular Amphotericin B in four patients (3 with *Crypotococcus neoformans* and 1 with *Coccidioides immitis* infections).[15] Three of these patients improved after 21–74 injections into the SRP; one failed to respond and died of overwhelming

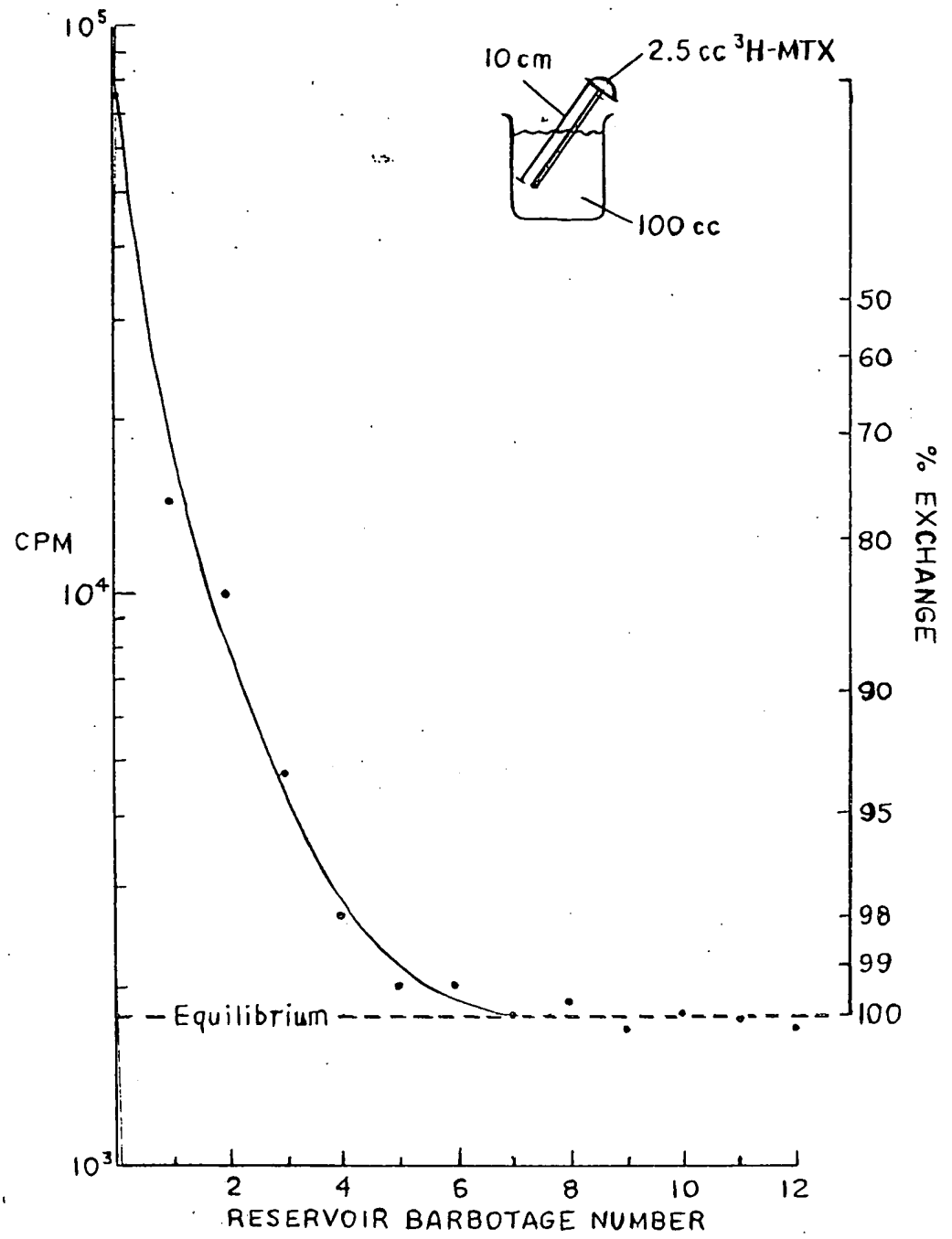

FIG. 2. Graph showing equilibration of 2.5 cc of tritium-labeled methotrexate (^{3}H-MTX) with a 100-cc isotonic saline resevoir (representing the maximum volume of ventricular CSF) after seven to eight pumps of the SRP device.

crytococcal meningitis after 12 injections. Subsequently, Diamond *et al.* provided more data on 21 patients and noted that of the 6 patients whose improvements were clearly due to the intraventricular chemotherapy, none had associated ventriculoatrial or ventriculoperitoneal shunts placed. On the basis of isotope ventriculography, they suggested that rapid outflow of intraventricular Amphotericin B via the shunt could have produced inadequate CSF drug levels, thus explaining the poorer results in the 9 out of 21 patients with shunts.[16]

Meningeal leukemia and carcinomatosis

When the SRP was introduced, methotrexate administered intrathecally for the therapy of meningeal leukemia and meningeal carcinomatosis had become accepted as standard therapy but with somewhat unpredictable results.[17] The availability of this device enabled a direct test of the hypothesis that intraventricular route of administration would be superior to the standard lumbar spinal route used hitherto. Our first experience with this approach was published in 1968 and soon led to a number of other investigations.[18] Thus, Shapiro *et al.* reported on a study of the CSF distribution and kinetics of methotrexate after intravenous, intrathecal (lumbar spinal tap) and intraventricular administration (via the SRP) in 21 patients with meningeal leukemia or carcinomatosis.[19] They found that the SRP route more consistently produced adequate CSF distribution of methotrexate than lumbar intrathecal injections. Kud *et al.* were able to use the SRP device in a careful study of the proliferative kinetics of the CNS leukemia cells in the CSF, and showed that such cells may proliferate very slowly and at different rates in different patients, thus providing one explanation of why it is difficult to eradicate CNS leukemia utilizing cell-cycle-specific chemotherapeutic agents.[20] In 1978, Spiers *et al.* reported on the use of the SRP in 23 patients with acute leukemia and 2 patients with malignant lymphoma. In 9 of the leukemic patients, the SRP was used for prophylaxis of meningeal leukemia and only 1 of these patients developed CNS leukemia. Because prophylaxis could also be achieved using less invasive techniques, these authors did not recommend the use of the SRP solely for prophylaxis. When use in therapy for existing meningeal leukemia, they reported excellent control of overt CNS leukemia and recommended the use of such devices for established meningeal leukemia or lymphoma.[21]

The problem of neurotoxicity associated with intrathecal methotrexate was tackled by Bleyer *et al.* in collaboration with our group at NIH, and this work led to the development of a significantly less toxic regimen when the drug was given in a "concentration × time" paradigm. Thus, single injections of 12 mg/m^2•dose were more toxic than repeated low-dose injections of 1 mg every 12 h for 3 days without any difference between the two treatment groups in the rate of remission induction, relapse rate, or remission duration.[22] Bleyer and Poplack also showed in a separate study that intraventricular methotrexate therapy was significantly more effective against meningeal leukemia than the same therapy given by lumbar puncture. Thus, the median CNS remission duration was 475 days versus 286 days for therapy via the ventricular and lumbar routes, respectively, and the rate of CNS relapse was reduced from 2.94 relapses/1000 days at risk during lumbar intrathecal therapy therapy to 0.93 relapses/1000 days of intraventricular therapy.[23] These results were supported by the work of Haughbin and Galicich in terms of the safety and efficacy of the use of the SRP device for CNS leukemia, but they emphasized that its superiority over the lumbar intrathecal method for prophylaxis had not been proved.[24] The pharmacokinetics of methotrexate given either intravenously or intraventricularly was further studied with the SRP technique in 13 children with acute lymphocytic leukemia and in 3 with non-Hodgkin's lymphoma by Ettinger *et al.* After receiving intraventricular methotrexate, patients with overt CNS leukemia retained methotrexate in the CSF significantly longer than patients treated prophylactically. This phenomenon was probably related to abnormal transport of the drug out of the CSF in the patients with CNS involvement, and these authors suggested that this increased the chances for both toxicity and therapeutic benefit.[25] DeVries *et al.* treated 25 consecutive adult patients with acute lymphocytic leukemia; 22 received prophylactic intraventricular methotrexate using the SRP technique. Two of the 22 experienced a CNS relapse and required additional treatments. Median survival was 38 months for all these adult patients and the quality of life was reported to be good.[26]

Use of the SRP in meningeal carcinomatosis has been less frequently reported. Thus, Mehta *et al.* showed that although Leucovorin given intravenously to patients receiving intraventricular methotrexate via the SRP device does not increase the CSF concentrations of "rescue" folate above those of CSF methotrexate, it does allow *serum* "rescue" folate to operate against and reduce the sytemic toxicity of methotrexate which may follow its intraventricular administration.[27] The management of an eosinophilic meningitis with Reed-Sternberg cells in a case of Hodgkin's lymphoma in systemic remission was reported by Hollister *et al.* Their patient responded to methotrexate

given intraventricularly via the SRP. When systemic relapse occured 6 months later, the CSF remained free of recurrent disease.[28] An excellent recent review of the use of the SRP in CNS malignancies treated at the Royal Marsden Hospital by Jacobs *et al.* will be further discussed in the section on complications.[63]

Solid neoplasms of the CNS

The demonstration by Mayer, Maickel, and Brodie in 1959 that lipid insoluble and highly organized organic molecules can pass by diffusion from CSF into brain while the blood-brain barrier limits movement of such substances from the brain into the blood was a stimulus to our group also to begin the use of the SRP device in malignant gliomas and other "inoperable" brain tumors.[29,30] Initially, we developed CSF perfusion techniques employing methotrexate and a variety of input-output channels, e.g., tumor bed to opposite or ipsilateral ventricle, ventricle to ventricle, and ventricle to lumbar CSF space. Of these the most practical was the ventricle-to-lumbar route.[4,5] We were satisfied with the relative safety of the method and the lack of systemic toxicity but we could not demonstrate antitumor efficacy. Unlike circulating blood, which permeates most of the solid tumor (excluding necrotic zones), the CSF will carry drugs into tumors by diffusion and only from those surfaces that are exposed to the CSF. Thus, potentially long periods of CSF perfusion may be required to produce cytotoxic drug concentrations in the tumor tissues. Conversely, it may not be possible to obtain sufficient concentrations, even with chemotherapeutic perfusion via the vascular route, because the blood-brain concentration gradients and protein binding that occur intravascularly may restrict drug passage into the tumor.[31]

Two approaches have evolved to circumvent these problems. The first was a further evolution of the subcutaneous drug reservoir and pump which began in 1970 when Henry Buchwald, Richard L. Varco, Perry L. Blackshear, Jr., his son, Perry J. Blackshear, and Frank D. Dorman at the University of Minnesota School of Medicine designed an implantable refillable pump capable of continuous infusion of known volume and concentration of a drug into any body space.[3] This basic concept has been further redesigned and is now known as the Infusaid.[32] Initially developed and used for continuous infusions of intravenous heparin, the use of this device has been extended to provide continuous and bolus doses of various chemotherapeutic agents (BCNU, FUdR, and DCMTX) by implanting the Infusaid into an intraarterial catheter (placed in the internal carotid artery). This has been performed in six patients with malignant astrocytomas.[33] No vascular complications were reported, but the clinical data are too scanty to allow further evaluation.

We sought to develop another approach that would avoid the risks of intraarterial perfusion and instead provide direct access to the extracellular environment of malignant gliomas while seeking to obviate the necessity for the ventricular or subarachnoid space to be in direct communication with the tumor bed. This invention is named the tumor cyst device (TCD) and is illustrated in Fig. 1A where it is shown connected to the SRP. It is available in different sizes selected to be at least 50% of the volume of the residual cavity left after glioma debulking has been completed. Experience with this device in over 40 patients with malignant glioma treated with local chemotherapy (using 8-azaguanine) and in 5 patients given local immunotherapy (using PPD) has shown the TCD to be an effective addition to the SRP which serves to maintain an intratumoral cavity thus facilitating local drug delivery to the tumor surfaces. Because the TCD is introduced at the time of maximal tumor debulking, the residual tumor seldom extends for more than 1 cm beyond the exposed surfaces. This is the major theoretical advantage of this device over intraventricular or subarachnoid chemotherapy for malignant gliomas. Although only Phase-I and pilot studies have been completed, the data are encouraging. Thus, over 75% of 40 patients receiving local 8-azaguanine via the SRP/TCD system survived more than 2 years and 2 are still alive and fully functional at 8 and 15 years post initiation of therapy.[14,34,35]

Intrathecal morphine for pain control in cancer patients

J.K. Wang was apparently the first investigator to report the successful use of intrathecally administered morphine for the relief of intractable pain due to cancer.[36] This was a significant ad-

vance in pain management for such patients in whom systemic narcotics usually allow relief only at dose levels also causing somnolence and inactivity. Initial treatments given by lumbar spinal tap were soon replaced by attempts to develop permanent indwelling systems for chronic use. At the same time, attempts were also made to substitute epidural catheter placment in order to avoid potential risk for meningitis. Thus, Poletti *et al.* reported on the use of the Broviac catheter as a partially indwelling system, and also on a completely implanted system consisting oa a large reservoir of morphine coupled via "on-off" and Hakim valves to an epidural catheter for pain relief in two cases.[38,39] Because of a number of reports in the literature on severe respiratory depression after small doses of epidural morphine, other workers began testing the effect of intrathecal injections. This was supported by the demonstration that bolus injections of 1 mg of morphine intrathecally caused no detectable morphine to appear in the blood whereas epidural injections of the same amount caused rapid appearance of the narcotic in the blood.[40] It should also be noted, however, that practically all of the reports of respiratory depression following epidural or intrathecal narcotics were on postoperative patients without preexisting tolerance to the narcotics and who also received a general anesthetic, immediately prior to or concurrently with, the intrathecal or epidural narcotic. Onofrio *et al.* reported the first use of the Infusaid pump system with an indwelling spinal pain relief at 1.8 mg/day.[41] Greenberg *et al.* also tested this technique but found that in their patients morphine dosage had to be increased quite rapidly to 150 mg/day.[42] It is obvious, therefore, that intrathecal narcotics do not eliminate the problem of tolerance, but this method does appear to produce analgesia no matter where the pain is located with a markedly lesser propensity to cause somnolence and inactivity. We have recently begun testing a simple modification of the SRP device coupled with a spinal catheter which can be implanted percutaneously through a Touhy needle, thus forming a totally implantable system with which the patient can be instructed to self-administer the intrathecal morphine. This is facilitated by placing the SRP device just inferolateral to the anterior-superior iliac spine where it can be easily reached for self-injection and manual barbotage. In preliminary experiences on two patients we have achieved excellent pain relief with twice a day injections at doses ranging between 10–30 mg/day. Both patients were transformed from being bedridden to being able to ambulate and perform most activities of daily living.[43]

Management of unresectable cystic tumors

The SRP device has been used in a few cases of unresectable cystic tumors, primarily craniopharyngiomas. Gutin *et al.* have reviewed their experience in four cases and conclude that the technique is safe and provides a reasonable alternative for symptomatic relief when total resection is not possible. They also recommended this method for additional local radiotherapy using intracystic isotopes as previously reported by Trippi *et al.* and by Backlund.[44,45,46] The symptomatic relief obtained by outpatient tumor cyst drainage via the SRP is often quite dramatic, as in a recent case wherein slowly developing bitemporal hemianopia could be suddenly "cured" by drainage of 5–6 cc of cyst fluid.[47] Use of isotope radiotherapy is usually reserved for cases in which the cyst fluid rapidly reaccummulates at increasingly shorter intervals after drainage. Goedhart has also recommended the use of injections of 10% saline to inhibit rapid cyst refilling.[64]

Other cystic tumors which have been managed in this fashion include an intramedullary epidermoid cyst of the conus medullaris[48] and a symptomatic Rathke's cleft cyst.[49]

Cytologic and pharmacologic monitoring of CSF

This application of the SRP device is an important aspect in the management of CNS neoplasia. We have used monthly cytologic evaluation for tumor cells in our series of patients treated with local chemotherapy using the SRP-TCD system. In most cases, detection of tumor cells from resevoir aspirates done prior to chemotherapy preceded symptomatic worsening and change in the CT scan appearance.[14] Mayer and Watson reported an unusual case of a 21-year-old woman with disseminated histiocytic lymphoma in whom cytologic monitoring played a key role in her 6.5 years of survival. Remissions and exacerbations of the tumor were accurately detected by periodic cytologic

examinations of 78 CSF specimens during the course of her treatment with total brain irradiation and combination chemotherapy.[50]

Pharmacologic assays of drug levels and their clearances in ventricular CSF drawn from the SRP device have also been of significant value. Thus, Maguire *et al.* point out that to control neurotoxicity of intrathecal chemotherapy, e.g., with methotrexate, it is important to determine precise drug concentrations. They draw attention to a sampling error that may be caused by retention of high drug concentrations in the resevoir as proved by *in vitro* experiments. Simple flushing (7 ×) of the resevoir with 3–5 cc of CSF withdrawn prior to drug injection corrects this source of sampling error.[51] Stewart *et al.* studied the penetration of PALA [*N*-)phosphonacetyl)-L-aspartate] into the brain and CSF when given i.v. in patients with malignant brain tumors. Concentrations of PALA in the CSF reached a peak in 8 h after i.v. infusion (= 12–40% of plasma concentration) and concentration in resected tumor tissue was greater than or equal to levels in temporalis muscle biopsies. Concentration of PALA in edematous brain adjacent to tumor was always lower than either tumor or muscle tissue levels.[52]

Experimental applications

In 1972 an experimental model for CSF pressure monitoring was developed in the rhesus monkey utilizing a spinal subarachnoid catheter connected to a SRP device placed over the lumbodorsal fascia. This model was developed in our laboratory for the specific use of Dr. W.F. Caveness, who was conducting a long-term study on the effect of x-irradiation on the spinal cord.[53] A few years later, working with J. Wood and D. Poplack, we extended this model by placing a catheter into the fourth ventricle via the cisterna magna and connecting it to a SRP device placed below the scalp. This latter model has been extensively used in pharmacologic and physiologic studies on the neurobiology of the CSF as well as in the evaluation of intraventricular and intrathecal chemotherapy after confirming its validity as a model for human CSF pharmacokinetics for methotrexate.[54,55] We have also used this model in a study of beta-lactam antibiotics and showed that the rhesus monkey CSF pharmacokinetics for ampicillin is consonant with published data on humans with normal meninges. The potential value of this model for pharmacologic trials in infectious diseases involving the CNS was also suggested.[56]

COMPLICATIONS

In earlier evaluations of the risks and complications of implanted resevoirs a very significant number of cases were noted, primarily as infections.[9,16,37] However, as emphasized by Posner and others, many of the noninfectious complications can be avoided by greater experience and by learning of proper SRP technique.[8,19,64] Similarly, careful attention to aseptic precautions during each use of the resevoir can significantly lower the risk of infection from the overall figure of 8–10% given in 1968.[9] The most common reasons for resevoir failure are plugging of the catheter by proteinaceous material, especially in cases where protein concentrations in the CSF are abnormally elevated and migration or misplacment of the ventricular catheter tips into brain tissue. The commonest infections are by staphylococcus epidermidis, and Sutherland *et al.* have reported on how it is possible to sterilize the resevoir with vancomycin without having to remove the SRP system.[58] We have utilized this technique ourselves with good results, and Connors has recently reported on a combination of vancomycin and rifampin in achieving cure of a staphylococcus epidermidis ventriculitis without SRP removal.[59] Other and less common complications associated with the use of the SRP have also been recognized. Thus, Bleyer *et al.* reported on two cases, in one of which a mass of tumor cells grew around the catheter of a SRP used to treat a patient with meningeal Burkitt's lymphoma. In the other case the catheter tip migrated into the contralateral thalamus. Both of these cases had methotrexate-associated leukoencephalopathy at autopsy. They implicated the misplaced catheter in this complication.[60] This was also emphasized by Packer *et al.*, who reported one case in which a CT scan showed a low-density mass surrounding the tip of the catheter associated with onset of aphasia and hemiplegia. A second case developed such a lesion in spite of repositioning

of the catheter prior to giving intraventricular methotrexate. Catheter removal and systemic steroids relieved the symptoms.[61] It should be noted however that Spiers *et al.*, in reviewing 23 patients with acute leukemia and two with malignant lymphoma receiving intraventricular chemotherapy via the SRP, concluded that the leukoencephalopathy was attributable to x-irradiation and use of cytotoxic drugs rather than to catheter-tip trauma.[21]

Katzner *et al.* have described one case of skull necrosis in a patient who received simultaneous radiotherapy and chemotherapy via the SRP.[62]

In a very balanced review of their experience with 27 SRPs installed in 24 patients with CNS neoplasia (mostly meningeal leukemia) at the Royal Marsden Hospital by Jacobs, Clifford, and Kay, complications were subdivided into those occurring with resevoir insertion and those with intraventricular chemotherapy. The former included three cases of failure to function either due to improper placement in extraventricular locations (sometimes associated with focal lesions and neurologic deficits) or due to wound infection with or without meningitis. Chemotherapy associated complications included seizure in one case that was easily controlled with anticonvulsants and thus did not interfere with chemotherapy and leukoencephalopathy which was noted in one case.[63]

CONCLUSIONS AND FUTURE APPLICATIONS

The most recent and extensive review of the use of the subcutaneous resevoir and pump is embodied in an M.D. thesis by Goedhart, who surveyed the results of 110 SRP devices implanted in 98 patients in Leiden, Holland. Infections occurred in only 9 patients in this series. He recommends the use of this device in the control of raised intracranial pressure, drainage of unresectable cystic craniopharyingiomas, as well as in its more common use for the treatment of CNS neoplasia.[64] We agree with the conclusion of Jacobs, Clifford, and Kay that the SRP "is a beneficial aid in the management of CNS disease in cases of acute lymphoblastic leukemia and acute myeloblastic leukemia. It may also be the optimal way of giving palliative treatment for lymphoid blast crisis of chronic granulocytic leukemia and other solid tumors involving the CNS where the systemic disease is likely to be the fatal determinant."[63] We would also like to recommend the use of the SRP-TCD system for local chemotherapy of solid primary malignant tumors of the CNS, e.g., astrocytomas Grades III and IV. The review of implantable drug-delivery systems by Blackshear and the reports of Phillips *et al.* on regional arterial perfusion also suggests the possibility of combining both intravascular and intrathecal local chemotherapy in the more recalcitrant malignant neoplasms of the CNS such as the glioblastoma multiforme.[3,14,33]

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